INVESTIGATING THE BLOOD COMPATIBILITY OF METALLOCENE POLYETHYLENE SUBJECTED TO STEAM TREATMENT

AGNES ARUNA JOHN

UNIVERSITI TEKNOLOGI MALAYSIA

INVESTIGATING THE BLOOD COMPATIBILITY OF METALLOCENE POLYETHYLENE SUBJECTED TO STEAM TREATMENT

AGNES ARUNA JOHN

A thesis submitted in fulfilment of the
requirements for the award of the degree of
Master of Philosophy (Biomedical Engineering)

Faculty of Biosciences and Medical Engineering

Universiti Teknologi Malaysia

JANUARY 2016

I dedicate this thesis to my beloved family:

My dearest parents, Mr. A John & Mrs. M Pauline Mary

ACKNOWLEDGEMENT

First of all, I wish to give my highest praise to God for giving me blessings and strength to complete this research. My deepest gratitude to my research supervisor, Dr. Saravana Kumar Jaganathan, Universiti Teknologi Malaysia (Faculty of Biosciences and Medical Engineering, UTM) for his continuous encouragement, guidance and support throughout my study and also to my co-supervisors Prof. Ida Idayu Muhamad (Faculty of Chemical Engineering, UTM) and Dr. Ahmad Zahran Md Khudzari (Faculty of Biosciences and Medical Engineering, UTM).

My sincere appreciation goes to dean of Faculty of Biosciences and Medical Engineering, Prof. Dr. Jasmy bin Yunus and the IJN-UTM cardiovascular engineering center director Prof. Dr-Ing. Eko Supriyanto for their constant support in helping me to complete my research.

I would like to acknowledge Mr. Yong Lee Ming and Miss. Farah Nadiya binti Muhamad Sobri, MSI Technologies, Malaysia for their support to use Hirox 3D digital microscope KH-8700, and the Lab technicians of UTM for their assistance.

I am very thankful to my lab-mates: Aruna Priyadharshni S, Muthu Vignesh V, Arunpandian B for their continued support. I am grateful to all faculties and non-teaching staffs of UTM.

This thesis would not have been possible without the unconditional support and love from my parents, Mr. A. John and Mrs. M. Pauline Mary. I would like to thank my brother Mr. J. Arokia Arun for being a constant source of motivation and encouragement.

Finally, my sincere appreciation goes to all my friends for their constant support in helping me complete my research work and writing of this thesis.

ABSTRACT

In this study, one of the green surface modification techniques, steam treatment was employed to improve the surface characteristics and haemocompatibility of metallocene polyethylene (mPE). The mean contact angle of untreated mPE (87.4º) decreased sharply for steam exposed mPE (60.25º). The increased surface roughness was demonstrated by atomic force microscopy (AFM), scanning electron microscopy (SEM) and Hirox 3-D microscopy. The mean roughness (Ra) of control mPE (2.757 nm) was increased to 8.753 nm by steam treatment, showed enhanced hydrophilicity. Fourier transform infrared spectroscopy (FTIR) analysis illustrated no chemical changes but the changes in absorbance intensity ensures the morphological changes in the treated samples. The blood compatibility studies were assessed by coagulation assays, haemolysis and platelet adhesion tests. The coagulation assays indicated a delay in clotting time on the steam exposed surface whereas haemolysis and platelet adhesion were significantly reduced. The green surface modification of mPE using steam enhanced its surface properties and haemocompatibility. The improved blood compatibility of mPE may help in efficient designing of haemocompatible biomaterials like cardiovascular implants.

ABSTRAK

Dalam kajian ini, salah satu teknik pengubahsuaian permukaan semula jadi iaitu rawatan wap telah digunakan untuk meningkatkan ciri-ciri permukaan dan keserasian darah metallocene polyethylene (mPE). Min sudut untuk stim tidak dirawat mPE (87.4º) menunjukkan penurunan mendadak selepas rawatan stim untuk mPE (60.25º). Peningkatan kekasaran pada permukaan ditunjukkan dengan kekerasan mikroskop atom (AFM), mikroskop imbasan elektron (SEM) dan Hirox 3-D mikroskop. Min kekasaran (Ra) kawalan MPE (2.757 nm) telah meningkat kepada 8.753 nm oleh rawatan stim, menunjukkan hidrofilik dipertingkatkan. Fourier spektroskopi inframerah (FTIR) analisis menunjukkan tiada sebarang perubahan kimia tetapi perubahan keamatan kuantiti menunjukkan perubahan morfologi dalam sampel yang telah dirawat. Kajian keserasian darah dinilai menerusi ujian pembekuan, hemolisis dan ujian lekatan platelet. Masa pembekuan darah di permukaan stim ditangguhkan, hemolisis dan platelet melekat telah berkurang dengan ketara. Pengubahsuaian permukaan melalui kaedah semula jadi untuk mPE menggunakan rawatan stim telah meningkatkan ciri-ciri permukaan dan keserasian darah. Keserasian darah yang bertambah baik dengan mPE boleh membantu dalam mereka bentuk bahan keserasian darah seperti kardiovaskular implan.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ATR-FTIR	-	Attenuated total reflectance fourier transformed infrared spectroscopy
3T3	-	3-day transfer, inoculum 3 × 105 cells
AFM	-	Atomic force microscopy
APTT	-	Activated partial thromboplastin time
BEL-7402	-	Hepatoma cells
CAGR	-	Compound annual growth rate
HA	-	Hydroxyapatite
HA	-	Haemolysis assay
HCL	-	Hydrochloric acid
LLDPE	-	Linear low density polyethylene
MC3T3-E1	-	Preosteoblast cell line
mPE	-	Metallocene polyethylene
NaOH	-	Sodium hydroxide
NW-PET	-	Non-woven polyethylene terephthalate
PANi	-	Polyaniline
PANi-AgNp	-	Polyaniline-silver nanoparticle
PC	-	Phosphatidylcholine
PCU	-	Polycarbonateurethane

PDMS	-	Polydimethylsiloxane
PEG	-	Polyethylene glycol
PEGMAs	-	Poly(ethylene glycol) monoacrylates
PEO	-	Poly(ethylene oxide)
PGS	-	Poly(glycerol sebacate)
PMMA	-	Poly(methyl methacrylate)
PP	-	Polypropylene
PRP	-	Platelet rich plasma
PT	-	Prothrombin time
PTMC	-	Poly(1,3-trimethylene carbonate)
PU	-	Polyurethane
PVA	-	Poly(vinyl alcohol)
PVC	-	Poly vinyl chloride
RBCs	-	Red blood cells
SD	-	Standard deviation
SEM	-	Scanning electron microscopy
VWF	-	Von willebrand factor
WBCs	-	White blood cells
XRD	-	X-ray diffraction

LIST OF SYMBOLS

cm^{-1}	-	Per centimetre
cm^2	-	Square centimetre
g/mol	-	Grams per mole
Hz	-	Hertz
MPa	-	Megapascal
mL	-	Millilitre
mm	-	millimetre
m Torr	-	Millitorr
M	-	Molar
nm	-	Nanometre
Ra	-	Average roughness
W	-	Watt
w/v	-	Weight per volume
μL	-	Microlitre
μm	-	Micrometre

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 General Introduction

A biomaterial is any matter, or construct that interacts with the biological systems. Biomaterials possess biocompatibility which refers to the ability of a material to perform with an appropriate host response in a specific situation (Williams, 1999). Biomaterials can be derived either from nature or synthesized in the laboratory using a variety of chemical approaches utilizing metallic components, polymers, ceramics or composite materials. They are often used and/or adapted for a medical application, and thus comprise whole or part of a living structure or biomedical device which performs, augments, or replaces a natural function (Williams, 2009).

The recent report expresses the reality that by 2017, the estimated global market for biomaterials will be 88.4 billion US$ with a compound annual growth rate (CAGR) of 15% (Markets and Markets, http://www.marketsandmarkets.com/PressReleases/global-biomaterials.asp). Biomaterials broadly fall into the four main types, namely metals, ceramics, polymers and biological substances. The selection of a biomaterial depends on the surrounding environment where it will be implanted. The implanted material should not cause any adverse effects like allergies, inflammation and toxicity, either immediately after surgery or under post-operative conditions.

The surface modification of biomaterials is defined as the process of changing the surface properties of a biomaterial by altering its physical, chemical or biological properties different from the existing characteristics that found on the surface of a material. The surface modification techniques are classified into three major categories namely 1. Physico-chemical methods, 2. Mechanical methods and 3. Biological methods, with each method having different divisions.

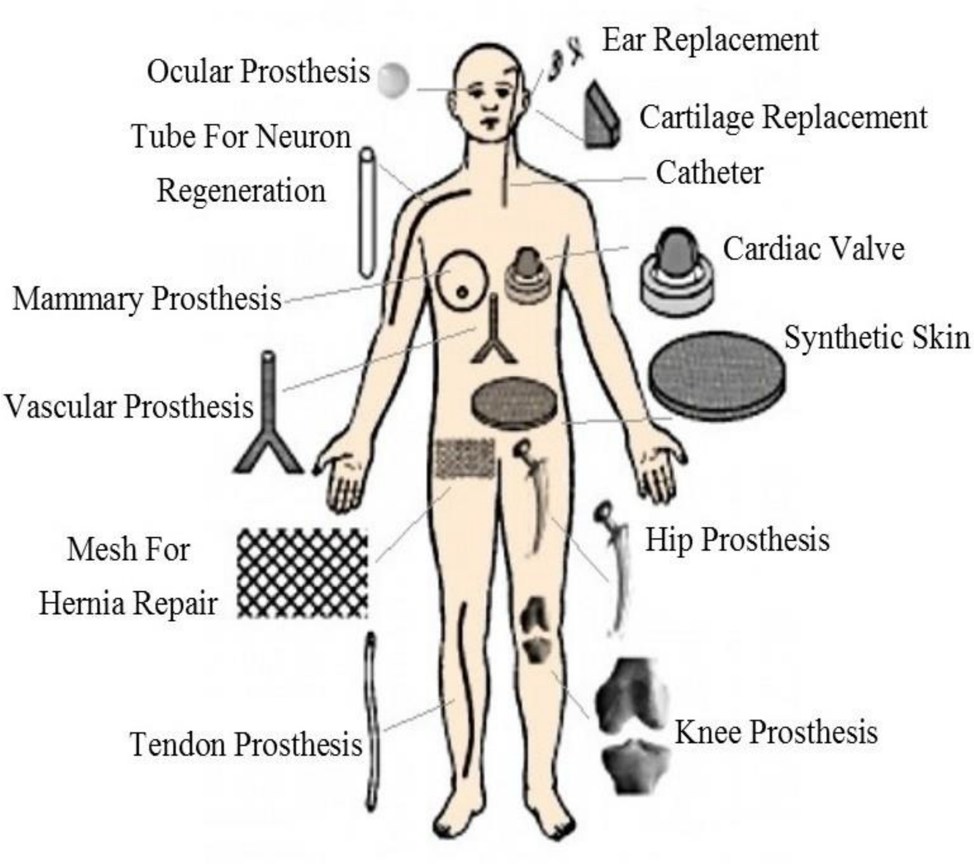

Figure 1.1: An example for the application of biomaterials

Among all four types, the polymers have widespread application in the field of biomaterials because of its excellent physico-chemical properties. The total North American market volume of polymers in medical devices totaled 1,370.0 million pounds, corresponding to revenues in excess of $1 billion. By 2018, revenues are expected to equal $1.45 billion, fuelled by a compound annual growth rate of 5.2 percent (http://www.frost.com/prod/servlet/press-release.pag?docid=266870643).

Table 1.1: Biomedical applications of polymers

Parts of the body	**Polymers used**
Ear and ear parts	acrylic, polyethylene, silicone, poly vinyl chloride (PVC)
Denture	acrylic, ultrahigh molecular weight polyethylene (UHMWPE), Polymethyl methacrylate
Facial prostheses	acrylic, silicone, nylon, Polyurethane, Polytetrafluoroethylene
Tracheal tubes	acrylic, silicone, nylon
Vascular grafts	Polytetrafluoroethylene, Polyethylene terephthalate.
Breast implants	Polydimethylsiloxane.
Heart valves	polyester, silicone, PVC
Pacemaker	polyethylene, acetal
Lung , Kidney and liver parts	polyester, polyaldehyde, PVC
Oesophagus segments	polyethylene, polypropylene (PP), PVC
Blood vessels	PVC, polyester
Orthopaedic implants	acrylic, nylon, silicone, PP, UHMWPE
Hip and knee joint replacements	Polyethylene, Polydimethylsiloxanes

New advancements in polymer technology to resolve this increasing demand of polymers in medical field inspired us to explore the existing metallocene polyethylene (mPE) that possess a variety of attractive performances like better tensile strength, elongation, toughness with excellent resistance to puncture, impact and bursting (Lipsitt, 1998). The excellent permeability to oxygen and excellent fence to ammonia and water makes metallocene polyethylene as a promising candidate for blood contacting devices and medical implants.

The foremost reason for the limitation of mPE in medical applications is the lacking of its blood compatibility (Mohandas *et al*., 2013) and so various surface modification techniques are being employed to improve the surface characteristics thereby enhancing the blood compatibility of metallocene polyethylene

The green surface modification using steam is non-toxic, non-corrosive controlled oxidation technique to modify the surface characteristics providing better biocompatibility with improved surface properties. Further, it's safer and eco-friendly which makes steam treatment technology as an attractive choice over the other treatments in surface modification of biomaterials (Feldbauer, 2007).

Steam treatment is interrelated with green chemistry, which does not involve in usage of any chemicals that encourages the design of products and its processes, thereby minimizing the use and production of hazardous substances or wastes. Since, steam is entirely pure it does not produce any harmful effect to the surface and also to the environment and no toxicity to human health (Lee *et al.*, 2013).

Generally, the surface modification of biomaterials can be performed especially for the biocompatibility enhancement, which is the most important feature while selecting a medical implant (Jaganathan *et al*., 2014b). For the first time, the mPE polymer was treated with steam, a gaseous state of water to enhance its blood compatibility. In this work, the surface characteristic changes along with blood compatibility of steam treated mPE were studied and documented.

1.2 Problem Statement

Blood compatibility is the foremost consideration for the medical implants. Although mPE has excellent physico-chemical and mechanical properties it fails as a promising biomaterial because of its poor bio and blood compatibility. Biocompatibility is a vital factor which determines the quality of a biomaterial and its application in various arenas. It may be defined as the ability of the material to perform at a specific region with the appropriate host reaction. The events occur when the blood comes in contact with the implant is collectively called as blood mediated reactions or blood compatibility.

Whenever the blood comes in contact with the implants (biomaterial) it will lead to following complications:

1. Blood component's interaction with surfaces resulting in protein and water absorption

2. Blood cells interfere with the surface of biomaterial and may result in destruction of blood cells and these actions lead to the haemostasis and coagulation.

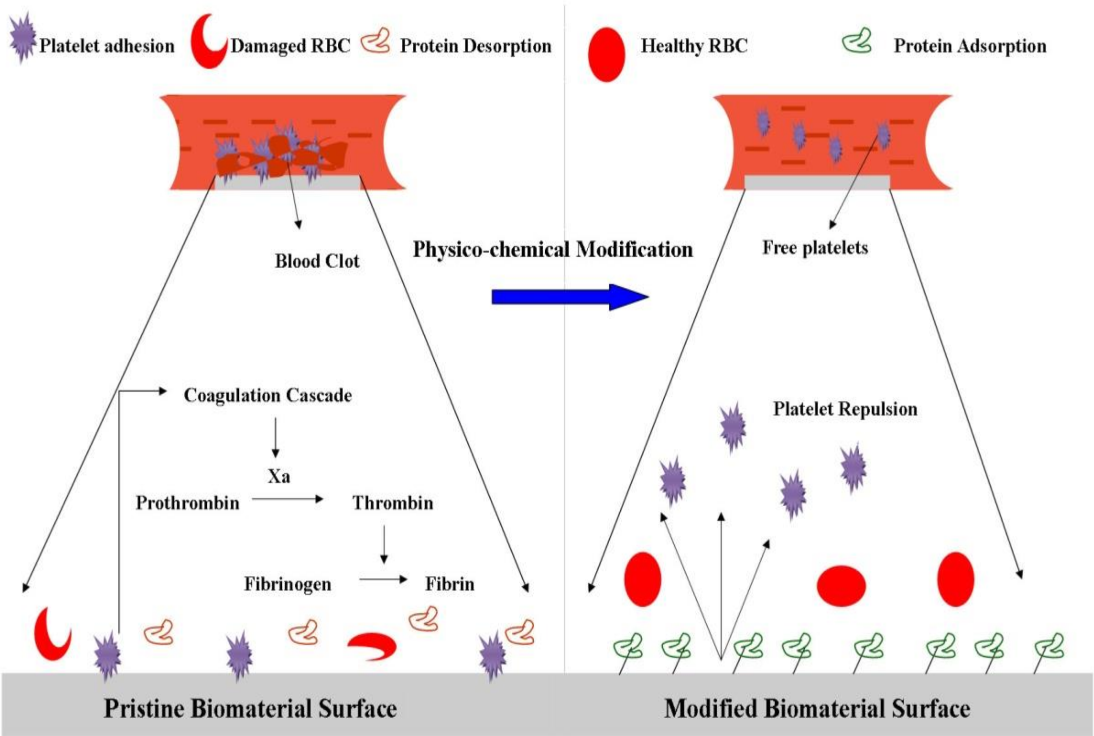

Figure 1.2: Blood compatibility problems resolved through surface modification (John *et al.*, 2015)

A promising biomaterial is one which does not elicit the above reactions. Hence, the biomaterials are subjected to surface modification to enhance its blood compatibility by eliminating the above mentioned complications

1.3 Objectives

1. To study the physico-chemical modifications of steam treated mPE and comparing it with the physico-chemical characteristics of untreated mPE.

2. To investigate the changes in the blood compatibility of the steam treated mPE surface.

1.4 Scope of the Research

The first part of the research was focused on the surface characterization of the metallocene polyethylene. The hydrophilicity of mPE was evaluated by means of contact angle measurements. The surface roughness were determined using scanning electron microscope (SEM), Hirox 3D microscopy and Atomic force microscopy (AFM). The chemical or functional group changes was investigated through Attenuated total reflectance fourier transform infrared spectroscopy (ATR-FTIR). The purpose of the surface characteristic study was to access the hydrophilicity and surface changes of mPE modified by the steam treatment

The second part of the study involved in blood compatibility studies of steam exposed metallocene polyethylene. The blood clotting time was estimated through Activated partial thromboplastin time (APTT) and Prothrombin time (PT). Haemolysis assay (HA) was performed to evaluate the destruction of red blood cells due to the implant material (mPE). The number of platelets adhered to the material surface was estimated by performing platelet adhesion test. The intention of this study is to evaluate the blood compatibility of steam exposed mPE.

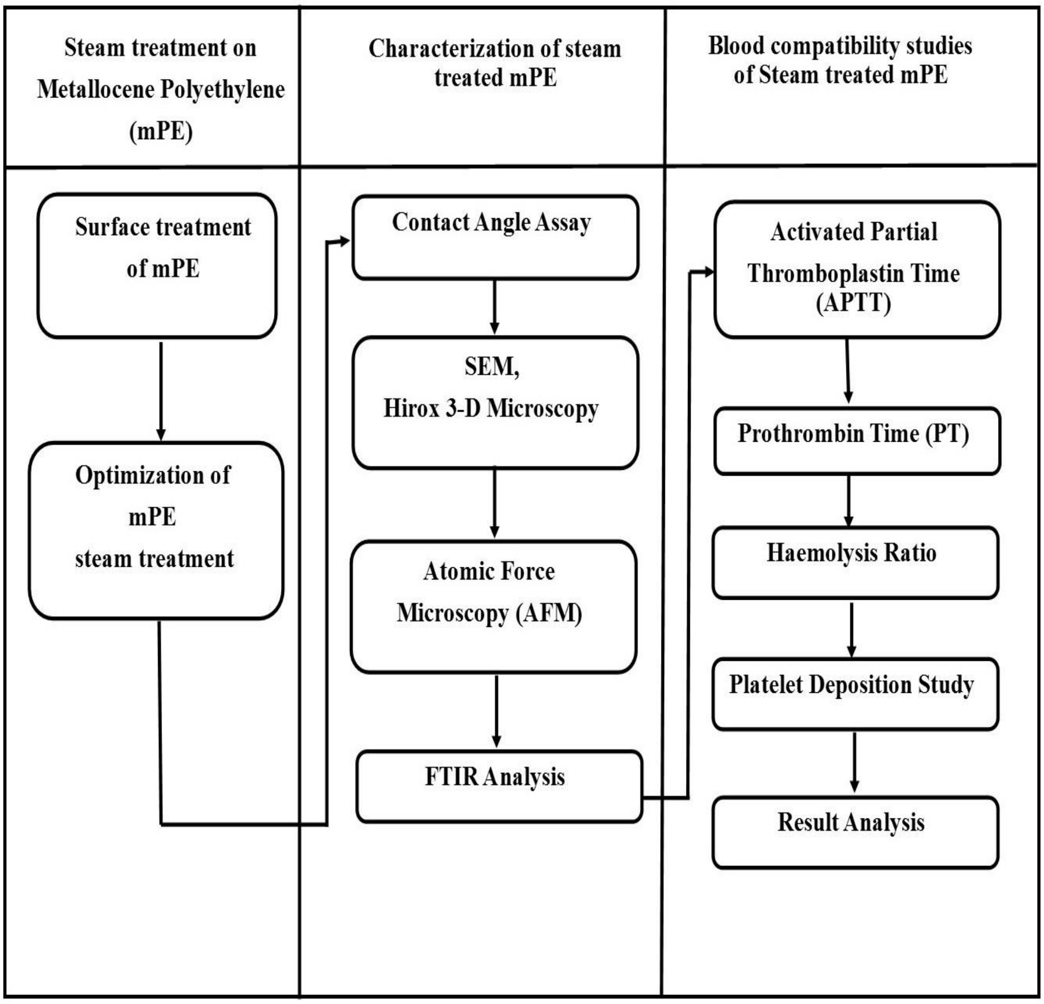

Figure 1.3: Scope of the Research

Lastly the steam induced metallocjuene polyethylene was studied in terms of both surface characteristics and blood compatibility studies.

1.5 Significance of the Research

This research provides a scope for the polymer implant manufacturers in producing the steam treated mPE implants possessing enhanced blood compatibility. Evaluating both the physico-chemical and blood compatibilty of the steam treated mPE helps in promoting the longevity of biomaterial implants.

Steam treatment is one of the green surface modification techniques that does not involve in usage or production of any chemicals or hazardous wastes. It is the most cost effective surface modification technique and also harmless method. Further, it’s safer and eco-friendly which makes steam treatment technology an attractive choice over the other treatments in surface modification for the blood compatibility enhancement.

REFERENCES

Agrawal, N. K., Agarwal, R., Awasthi, K., Vijay, Y. K. and Swami, K. C. (2014). Surface Modification of Nanocomposite Polymer Membranes by Ion Plasma Irradiation for Improving Biocompatibility of Polymer. *Adv. Mat. Lett.* 5 (11), 645-651.

Alves, P., Pinto, S., Ferreira, P., Kaiser J. P., Bruinink, A., de Sousa, H. C. and Gil, M. H. (2014). Improving Cell Adhesion: Development of a Biosensor for Cell Behaviour Monitoring by Surface Grafting of Sulfonic Groups onto a Thermoplastic Polyurethane. *J. Mater. Sci. Mater. Med.* 25(8), 2017-26.

Amarnath, L. P., Srinivas, A. and Ramamurthi, A. (2006). In Vitro Hemocompatibility Testing of UV-Modified Hyaluronan Hydrogels. *Biomaterials*. 27, 1416–1424.

Arima, Y. and Iwata, H. (2007). Effect of Wettability and Surface Functional Groups on Protein Adsorption and Cell Adhesion Using Well-Defined Mixed Self-Assembled Monolayers. *Biomaterials.* 28, 3074–3082.

Babiuch, K., Becer, C. R., Gottschaldt, M., Delaney, J. T., Weisser, J., Beer, B., Wyrwa, R., Schnabelrauch, M. and Schubert, U. S. (2011). Adhesion of Preosteoblasts and Fibroblasts onto Poly(Pentafluorostyrene)-Based Glycopolymeric Films and Their Biocompatibility, *Macromol Biosci.* 11, 535-548.

Balakrishnan B., Kumar, D. S., Yoshida, Y. and Jayakrishnan, A. (2005). Chemical Modification of Poly(Vinyl Chloride) Resin Using Poly(Ethylene Glycol) to Improve Blood Compatibility. *Biomaterials*. 26(17), 3495–3502.

Bergstrom, D. (2008). The Absorption of Laser Light by Rough Metal Surfaces. Ph.D. Thesis. Luleå University of Technology, Luleå, swedan.

Boretos J.W. and Eden, M. (1984). *Contemporary Biomaterials, Material and Host Response. Clinical Applications New Technology and Legal Aspects*. Noyes Publications, Park Ridge, 232–233.

Butruk, R., Trzaskowski, M. and Ciach, T. (2014). Cell Membrane-Mimicking Coating for Blood-Contacting Polyurethanes, *J Biomater Appl*. 29(6), 801-12.

Cao, Y., Chan, F., Chui, Y. H. and Xiao, H. (2012). Characterization of Flax Fibres Modified By Alkaline, Enzyme, and Steam-Heat Treatments. *Bio Resources*. 7, 4109-4121.

Cao, Y., Weng, J., Chen, J., Feng, J., Yang, Z. and Zhang, X. (1996) Water Vapour-Treated Hydroxyapatite Coatings after Plasma Spraying and Their Characteristics. *Biomaterials.* 17(4), 419-24.

Chang, H. I. and Wang, Y. (2011). *Regenerative Medicine and Tissue Engineering - Cells and Biomaterials: Cell Responses to Surface and Architecture of Tissue Engineering Scaffolds.* Intech publications, 1-21.

Chen, C. H., Lin, C. T., Hsu, W. L., Chang, Y. C., Yeh, S. R., Li, L. J. and Yao, D. J. (2013). A Flexible Hydrophilic-Modified Graphene Microprobe for Neural and Cardiac Recording. *Nanomedicine.* 9(5), 600-4.

Chung, T. W., Liu, D. Z., Wang, S. Y. and Wang, S. S. (2003). Enhancement of the Growth of Human Endothelial Cells by Surface Roughness at Nanometer Scale, *Biomaterials.* 24, 4655-4661.

Costa C. A. S. (2001). Testes de citotoxicidade em cultura de ce´lulas. In: Estrela C ed. *Metodologia cientı´fica: ensino e pesquisa em odontologia. Sa˜o Paulo: Artes Me´dicas* LTDA, 145–160.

Deligianni, D. D., Katsala, N. D., Koutsoukos, P. G. and Missirlis, Y. F. (2001). Effect of Surface Roughness of Hydroxyapatite on Human Bone Marrow Cell Adhesion, Proliferation, Differentiation and Detachment Strength. *Biomaterials.* 22, 87-96.

deMel, A., Cousins, B. G. and Seifalian, A. M. (2012). Surface Modification of Biomaterials: A Quest for Blood Compatibility. *Int J Biomater.*1-8.

Ebara, M., Kotsuchibashi, Y., Narain, R., Idota, N., Kim, Y. J., Hoffman, J. M., Uto, K. and Aoyagi, T. (2014). *Smart Biomaterials*. Springer.

Fedel, M., Motta, A., Maniglio, D. and Migliaresi, C. (2009). Surface Properties and Blood Compatibility of Commercially Available Diamond-Like Carbon Coatings for Cardiovascular Devices. *J. Bio. Mat. Res. B*. 90, 338–349.

Feldbauer, S.L. (2007) Steam Treating; Enhancing the Surface Properties of Metal Components. *Heat Treating Progress*, 51-55.

Feng, Y., Zhao, H., Behl, M., Lendlein, A., Guo, J. and Yang, D. (2013). Grafting of Poly(Ethylene Glycol) Monoacrylates on Polycarbonateurethane By UV Initiated Polymerization for Improving Hemocompatibility. *J. Mater. Sci. Mater. Med.* 24(1), 61-70.

Frost & Sullivan. (http://www.frost.com/prod/servlet/press-release.pag?docid=266870643) Retrieved date: 25 Apr. 2015.

Gentleman, E., Ball, M. D. and Stevens, M. M. (2009). *Medical Sciences* – Vol II – *Biomaterials*, EOLSS publishers, Oxford, UK.

Gorbet, M. B. and Sefton, M. V. (2004). Biomaterial-associated Thrombosis: Roles of Coagulation Factors, Complement, Platelets and Leukocytes. *Biomaterials*. 25, 5681–5703.

Hernández de Gatica, N. L., Jones, G. L. and Gardella, J. A. (1993). Surface Characterization of Titanium Alloys Sterilized for Biomedical Applications. *Appl. Surf. Sci.* 68, 107-121.

Hoang, E. M., Allen, N. S., Liauw, C. M., Fontan, E., Lafuente, P. (2006). The Thermo-oxidative Degradation of Metallocene polyethylenes. Part 1: Long-Term Thermal Oxidation in the Solid State. *Polym Degrad Stabil.* 91, 1356-1362.

Jackson, M. J., Robinson, G. M., Ali, N., Kousar, Y., Mei, S., Gracio, J., Taylor, H. and Ahmed, W. (2006). Surface Engineering of Artificial Heart Valve Disks Using Nanostructured Thin Films Deposited By Chemical Vapour Deposition and Sol-Gel Methods. *J. Med. Eng. Technol.* 30(5), 323–329.

Jaganathan, S. K., Balaji, A., Vellayappan, M. V., Subramanian, A. P., John, A. A., Asokan, A. K. and Supriyanto, E. (2015). Review: Radiation-induced Surface Modification of Polymers for Biomaterial Application, *J. Mater. Sci.* 50(5), 2007–2018.

Jaganathan, S. K., Mohandas, H., Sivakumar, G., Kasi, P., Sudheer, T., Veetil S. A., Murugesan, S. and Supriyanto, E. (2014a). Enhanced Blood Compatibility of Metallocene Polyethylene Subjected to Hydrochloric Acid Treatment for Cardiovascular Implants. *Bio. Med. Res. Int.* 2014, 1-7.

Jaganathan, S. K., Supriyanto, E., Murugesan, S., Balaji, A. and Ashokan MK. (2014b). Biomaterials in Cardiovascular Research: Applications and Clinical Implications. *Bio. Med. Res. Int.* 2014, 1-11.

Jensen, C., Gurevich, L., Patriciu, A., Struijk, J. J., Zachar, V. and Pennisi, C. P. (2012). Increased Connective Tissue Attachment to Silicone Implants By a Water Vapor Plasma Treatment. *J. Biomed. Mater. Res. Part A.* 100, 3400–3407.

John, A. A., Subramanian, A. P., Vellayappan, M. V., Balaji, A., Jaganathan, S. K., Mohandas, H., Paramalingam, T., Supriyanto, E. and Yusof, M. (2015). Review: Physicochemical Modification as a Versatile Strategy for Biocompatibility Enhancement of Biomaterials. *RSC Adv*. 5, 39232-39244.

Kashiwazaki, H., Kishiya, Y., Matsuda, A., Yamaguchi, K., Iizuka, T., Tanaka, J. and Inoue, N. (2009). Fabrication of Porous Chitosan/Hydroxyapatite Nanocomposites: Their Mechanical and Biological Properties. *Bio-Med. Mater. Eng.* 19, 133-140.

Kealy, T. J. and Pauson, P. L. (1951). A New Type of Organo-Iron Compound. *Nature.*168, 1039-1040.

Khanlou, H. M. (2012). FE-SEM and EDX Characterization of Sand Blasted and Sulfuric Acid Etched of Novel Biomaterial (Ti13Nb13Zr). *Aust. J. Basic Appl. Sci*. 6(6), 125-131.

Kostelijk, E. H., Klomp, A. J., Engbers, G. H., Gouwerok, C. W., Verhoeven, A. J., Van Aken, W. G., Feijen, J. and de Korte, D. (2001). Improved Platelet Compatiblity of Water Vapour Glow Discharge Treated Non-Woven

Poly(Ethylene Terephthalate) Leukocyte-Reduction Filters for Different Types of Platelet Concentrates. *Transfus. Med.* 11(3), 199-205.

Kozbial, A., Li, Z., Conaway, C., McGinley, R., Dhingra, S., Vahdat, V., Zhou, F., Liu, B. D. H. and Li, L. (2014). Study on the Surface Energy of Graphene by Contact Angle Measurements, *Langmuir*, 30, 8598-8606.

Lampin, M., Warocquier, C., Legris, C., Degrange, M. and Sigot Luizard, M. F. (1997). Correlation between substratum roughness and wettability, cell adhesion, and cell migration. *J. Biomed. Mater. Res.* 36, 99–108.

Laroussi, M. (1996). Sterilization of Contamination Matter with an Atmospheric Pressure Plasma. *IEEE Trans. Plasma Sci*. 24(3), 1188-1191.

Lee, H. C., Monji, M., Parsley, D., Sahimi, M., Liu, P., Egolfopoulos, F. and Tsotsis, T. (2013). Use of Steam Activation as a Post-treatment Technique in the Preparation of Carbon Molecular Sieve Membranes. *Ind. Eng Chem Res.* 52, 1122−1132.

Lee, J. H., Park, J. W. and Lee, H. B. (1991). Cell Adhesion and Growth on Polymer Surfaces with Hydroxyl Groups Prepared By Water Vapour Plasma Treatment. *Biomaterials.* 12(5), 443-8.

Li, L., Crosby, K., Sawicki, M., Shaw, L. L. and Wang Y. (2012). Effects of Surface Roughness of Hydroxyapatite on Cell Attachment and Proliferation. *J. Biotechnol. Biomater.* 2, 150.

Lim, J. Y. and Donahue, H. J. (2007). Cell Sensing and Response to Micro and Nanostructured Surfaces Produced By Chemical and Topographic Patterning. *Tissue Engineering.* 13(8), 1879-91.

Lim, J. Y., Hansen, J. C., Siedlecki, C. A., Runt, J. and Donahue, H. J. (2005). Human Foetal Osteoblastic Cell Response to Polymer-Demixed Nanotopographic Interfaces. *J. R. Soc. Interface.* 2, 97-108.

Lipsitt, B. (1998). Performance Properties of Metallocene Polyethylene, EVA and flexible PVC films. *J Plast Film Sheet*. 14 (3), 242–255.

Lipsitt, B. (1997). Metallocene polyethylene films as alternatives to flexible PVC film for medical device fabrication. *Proceedings of the Society of Plastics Engineers*

55th Annual Technical Conference. May. SPE, Brookfield, Conn, USA, 2854–2858.

Liu, P., Chen, Q., Yuan, B., Chen, M., Wu, S., Lin, S. and Shen, J. (2013a). Facile Surface Modification of Silicone Rubber with Zwitterionic Polymers for Improving Blood Compatibility. *Mater Sci Eng C Mater Biol Appl*. 33(7). 3865-3874.

Liu, X. L., Zhou, W. R., Wu, Y. H., Cheng, Y. and Zheng, Y. F. (2013b). Effect of Sterilization Process on Surface Characteristics and Biocompatibility of Pure Mg and Mgca Alloys. *Mat. Sci. Eng. C.* 33, 4144–4154

Liu, X., Yuan, L., Li, D., Tang, Z., Wang, Y., Chen, G., Chen, H. and Brash, J. L. (2014). Blood Compatible Materials State of the Art. *J. Mater. Chem. B*. 2, 5718-5738.

Markets and Markets. (http://www.marketsandmarkets.com/PressReleases/global-biomaterials.asp) Retrieved date: 14 Feb. 2015.

Milinkovi, I., Rudolf, Rai, R. T., Aleks, Z., Lazi, V., Todorovi, A., and Stamenkovi, D. (2012). Aspects of Titanium-Implant Surface Modification at the Micro and Nano Levels. *Mater. Technol.* 3, 251–256.

Miller D. C., Thapa, A., Haberstroh, K. M. and Webster, T. J. (2004). Endothelial and Vascular Smooth Muscle Cell Function On Poly(Lactic-Co-Glycolic Acid) with Nano-Structured Surface Features. *Biomaterials.* 25(1), 53-61.

Mohandas, H., Sivakumar, G., Palaniappan, K., Jaganathan, S.K. and Supriyanto, E. (2013). Microwave-Assisted Surface Modification of Metallocene Polyethylene for Improving Blood Compatibility. *BioMed Res Int*. 2013, 1–7

Nader, P., Zahra, H. and Mohammad, N. (2012). Fractography of Steam Treated Sintered Steel Compacts, Comat Recent Trends in Structural Materials. 1-6.

Nie, S., Xue, J., Lua, Y., Liu, Y., Wang, D., Sun, S., Ran, F. and Zhaoa, C. (2012). Improved Blood Compatibility of Polyethersulfone Membrane with a Hydrophilic and Anionic Surface, *Colloids Surf B*. 100,116–125.

Niinomi, M. (2002). Recent Metallic Materials for Biomedical Applications. *Metal. Mater. Trans. A.* 33, 477–486.

Nordin, N. I. A. A., Ariffin, H., Andou, Y., Hassan, M. A., Shirai, Y., Nishida, H., Yunus, W. M. Z. W., Karuppuchamy, S. and Ibrahim, N A. (2013). Modification of Oil Palm Mesocarp Fiber Characteristics Using Superheated Steam Treatment. *Molecules.* 18, 9132-9146.

Pacifici, E., Bossu, M., Giovannetti, A., Torre, G. L., Guerra, F. and Polimeni, A. (2013). Surface Roughness of Glass Ionomer Cements Indicated for Uncooperative Patients according To Surface Protection Treatment. *Annali di Stomatologia.* 4 (3-4), 250-258.

Pallister, C. and Watson, M. (2010). *Haematology.* Scion Publishing, Bloxham, 334–336.

Pattanaik, B., Pawar, S. and Pattanaik S. (2012). Biocompatible Implant Surface Treatments. *Indian J Dent Res.* 23(3), 398–406.

Prabhakar, P. K., Raj, S., Anuradha, P. R., Sawant, S. N., Doble, M. (2011). Biocompatibility Studies on Polyaniline and Polyaniline-Silver Nanoparticle Coated Polyurethane Composite. *Colloid. Surf. B.* 86, 146-153.

Rai, R., Tallawi, M., Roether, J. A., Detsch, R., Barbani, N., Rosellini, E., Kaschta, J., Schubert, D. W. and Boccaccini, A. R. (2013). Sterilization effects on the physical properties and cytotoxicity of poly(glycerol sebacate). *Mater. Lett.* 105, 32-35.

Razavi-Nouri, M. and Hay, J. N. (2004). Effect of Orientation on Mechanical Properties of Metallocene polyethylenes. *Iran Polym J.* 13(6), 521-530.

Razavi-Nouri, M. and Hay, J. N. (2001). Thermal and Dynamic Mechanical Properties of Metallocene polyethylene. *Polymer*. 42(21), 8621-8627.

Schmalz, G. (2002). Material Science: Biological Aspects. *J. Dent. Res.* 81, 660–663.

Silvio, L. D. (2008*). Cellular Response to Biomaterials*. (1st ed.) Woodhead Publishing: Elsevier, Cambridge.

Sinn, H. and Kaminsky, W. (1980). Ziegler-Natta Catalysis, *Adv. Organomet. Chem.* 18, 99-149.

Sirolli, V., Di Stante, S., Stuard, S., Di Liberato, L., Amoroso, L., Cappelli, P. and Bonomini, M. (2000). Biocompatibility and Functional Performance Of A Polyethylene Glycol Acid-Grafted Cellulosic Membrane for Hemodialysis. *Int J Artif Organs.* 23(6), 356-64.

Stevens, K. N. J. (2011). Blood-contacting Biomaterials for Critical Clinical Applications. Maastricht, 2011.

Thapa, A., Miller, D. C., Webster, T. J. and Haberstroh, K. M. (2003). Nano-Structured Polymers Enhance Bladder Smooth Muscle Cell Function, *Biomaterials*. 24(17), 2915-26.

Then, Y. Y., Ibrahim, N. A., Zainuddin, N., Ariffin, H., Yunus, W. M. Z. W. and Chieng, B. W. (2014). The Influence of Green Surface Modification of Oil Palm Mesocarp Fiber By Superheated Steam on the Mechanical Properties and Dimensional Stability of Oil Palm Mesocarp Fiber/Poly(Butylene Succinate) Biocomposite. *Int. J. Mol. Sci.* 15, 15344-15357.

Wang, H. J., Fu J. X. and Wang, J. Y. (2009). Effect of Water Vapor on the Surface Characteristics and Cell Compatibility of Zein Films. *Colloids Surf. B Biointerfaces*. 69(1), 109-15.

Wang, J, He, Y., Maitz, M. F., Collins, B., Xiong, K., Guo, L., Yun, Y., Wan, G. and Huang N.J. (2013). A Surface-Eroding Poly(1,3-Trimethylene Carbonate) Coating for Fully Biodegradable Magnesium-Based Stent Applications: Toward Better Biofunction, Biodegradation and Biocompatibility. *Acta Biomater*. 9, 8678–8689.

Williams, D. F. (1999). *The Williams Dictionary of Biomaterials*, Liverpool University Press: Liverpool, United Kingdom.

Williams, D.F. (2008). On the Mechanisms of Biocompatibility. *Biomaterials*. 29, 2941–2953.

Williams, D.F. (2009). On the Nature of Biomaterials. *Biomaterials.* 30, 5897-5909.

Xiang, T., Yue, W. W., Wang, R., Liang, S., Sun, S. D. and Zhao, C. S. (2013). Surface Hydrophilic Modification of Polyethersulfone Membranes by Surface-Initiated

ATRP with Enhanced Blood Compatibility. *Colloids Surf. B Biointerfaces*. 110, 15-21.

Xu, Q., Yang, Y., Yang, J., Wang, X., Wang, Z. and Wang, Y. (2013). Plasma Activation of Porous Polytetrafluoroethylene Membranes for Superior Hydrophilicity and Separation Performances via Atomic Layer Deposition of Tio2. *J. Memb. Sci*. 443, 62-68.

Yang, L., Davis, J. C., Vankayala, R., Hwang, K. C., Zhao, J. and Yan, B. (2010). Biocompatibility of Polymer Grafted Core/Shell Iron/Carbon Nanoparticles. *Biomaterials.* 31, 5083-5090.

Yang, K., Yu, W., Zhou, C. (2007). Thermal Oxidation of Metallocene-Catalyzed Poly(ethylene octene) by a Rheological Method. *J Appl Polym Sci.* 105, 846–852 (2007)

Zhang, B., Luo, Y., Pearlstein, A. J., Aplin, J., Liu, Y., Bauchan, G. R., Payne, G. F., Wang, Q., Nou, X. and Millner, P.D. (2014). Fabrication of Biomimetically Patterned Surfaces and Their Application to Probing Plant-Bacteria Interactions. *ACS Appl. Mater. Interfaces.* 6, 12467-78.

Zhuanga, P. Y., Lia,Y. L., Fanb, L., Linb, J. and Hu, Q. L. (2012). Modification of Chitosan Membrane with Poly(Vinyl Alcohol) and Biocompatibility Evaluation. *Int. J. Biol. Macromol* 50, 658–663.